IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: HAMAMOTO et al.
Serial No. 10/587,862
Filed: July 28, 2006
For: ANTI-INFLAMMATORY ANALGESIC FOR EXTERNAL USE

Art Unit: 1617
Examiner: Sahar Javanmard

DECLARATION

Honorable Commissioner for Patents
Sir

I, Hidetoshi Hamamoto, a citizen of Japan, declare and state as follows.

I am one of the co-inventors of the subject matter of the above-identified application and have complete knowledge of all aspect of the invention embodied therein.

I graduated from the engineering department of Tokushima University, Japan, in 1993, and completed the post graduate course in 1995.

In 1995, I was employed in Teikoku Seiyaku Co., Ltd. and engaged in a research and development work related to an external preparation such as a plaster etc.

After leaving Teikoku Seiyaku Co., Ltd. in 2002, I was employed in MEDRx Co., Ltd. Since then, I was engaged in a research of formulations such as an external preparation, or an oral jelly formulation etc., and a developing and manufacturing works.

I understand the English language and studied the Official Action dated April 14, 2009 received in said application. In order to compare an enhancing effect of lidocaine on transdermal absorption of etodolac (the present invention) with the said effect on transdermal absorption of diclofenac and ketorolac (Lee et al., US 7,166,641), the following experiment was carried out.

The following experiment was entirely directed and supervised by the inventor of the present invention, Hidetoshi Hamamoto.

1. Formulation

A plaster was selected as a formulation of transdermal administration and test formulations were prepared according to Product example 2 of the present specification. Each ingredient was weighed and mixed so that the ratio of ingredients was as shown in the table below.

[Table] Ingredients of the formulation (W/W %)

	Present Invention		Cited Invention			
	Eto-Lid	Eto (Control)	Dic-Lid	Dic (Control)	Ket-Lid	Ket (Control)
NSAID	Etodolac 5	Etodolac 5	Diclofenac 5	Diclofenac 5	Ketorolac 5	Ketorolac 5
Lidocaine	4	0	4	0	4.6	0
NSAID:Lid (mole ratio)	1:1		1:1		1:1	
Diethyl Sebacate	2	2	2	2	2	2
Macrogol	7	7	7	7	7	7
Glycerin	35	35	35	35	35	35
BHT	1	1	1	1	1	1
Liq. Paraffin	20	24	20	24	19.4	24
Polybutene	2	2	2	2	2	2
SIS5002	8	8	8	8	8	8
Arkon P-100	16	16	16	16	16	16
total	100	100	100	100	100	100

Eto: Etodolac, Mw=287.4,
Dic: Diclofenac, Mw=296.1,
Ket: Ketorolac, Mw=255.3,
Lid: Lidocaine, Mw=234.3

2. Method

A. Evaluation *in vitro*

A-1) Skin permeability test

Skin permeability was evaluated using a Franz-type diffusion cell.

The receptor chamber of the Franz cell was filled with a saline, and warmed at 32℃. An abdominal skin of male Wistar rat (5 weeks) was shaved at the previous day and extracted. The isolated abdominal skin of the Wistar rat was applied thereto. The test plasters were applied to the rat skin. At 2,

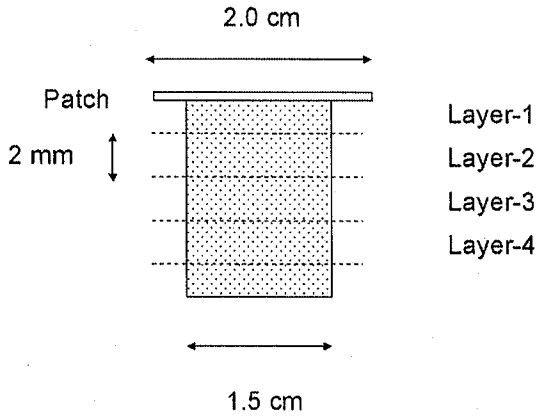
4, 6, 8 hours after the start of the test, 0.2ml of receptor fluid was sampled. The concentration of NSAID in the receptor solution is measured by HPLC.

A-2) Penetratability and Diffusivity test in muscle tissue

The method of the test example 1 described in the present invention has been modified and penetratability and/or diffusivity was evaluated in bovine muscle tissue.

First of all, the above-mentioned plaster preparations of the cited reference and the present invention were put on bovine muscle tissue (1.5×1.5×2 cm), and kept putting for 24 hours at 4℃ as shown by Fig.1. This tissue was sliced to four layers (each level 2 mm) to evaluate of diffusion property after 24 hours, and the drug concentration in each layer of the tissue was measured by HPLC.

Fig.1



B. Evaluation *in vivo*

The abdominal hair of male SD rat was shaved with an electrical clipper and shaver on the previous day of the experiment.

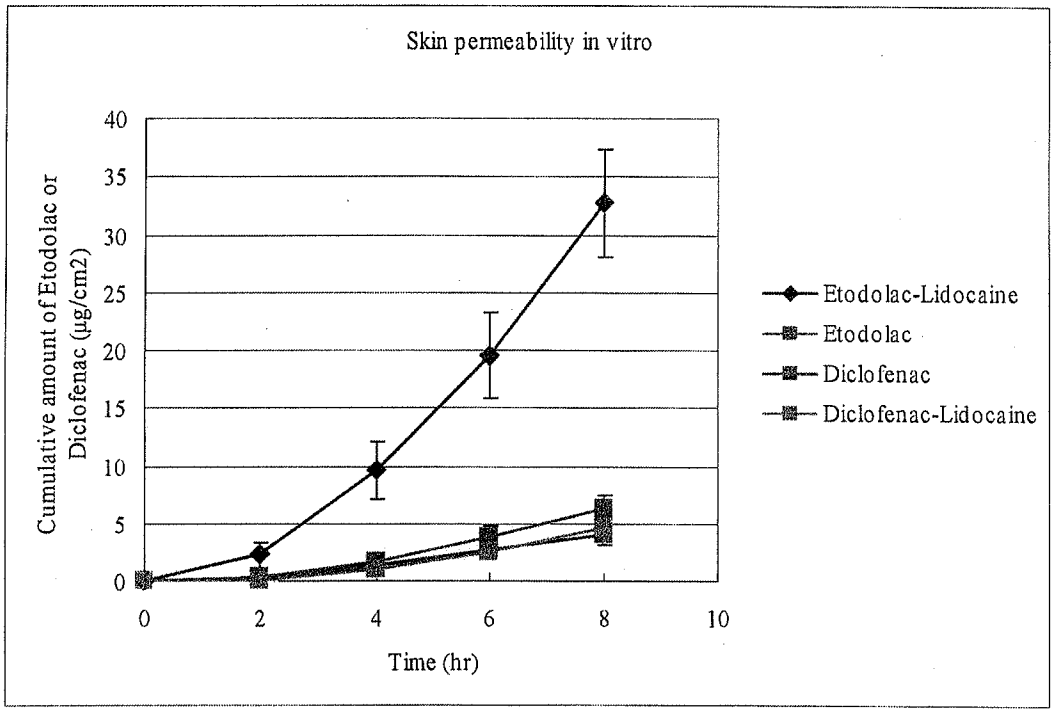
The above-mentioned plaster preparations whose diameter was 23 mm were applied to the abdomen of the rat, and after 4 or 8 hours, blood was collected and the abdominal tissue was cut off using a punch into a circular shape whose diameter was 18 mm.

The isolated tissue was separated into skin and muscle, and concentration of Etodolac and Diclofenac in the plasma and the muscle tissue were measured by HPLC.

3. Results

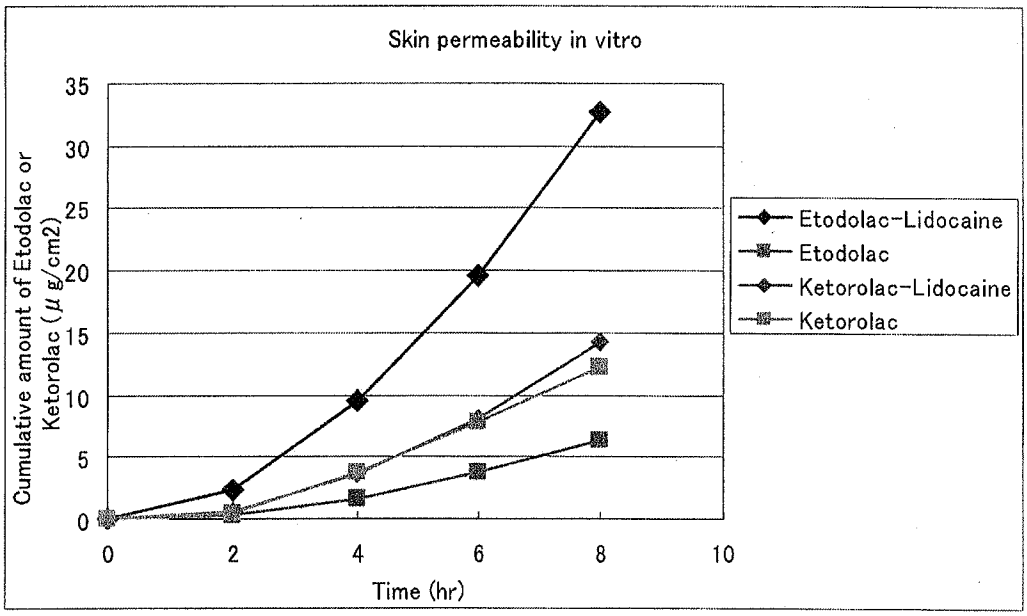
A-1) Skin permeability test

Comparison with Diclofenac



In the present invention, transdermal absorption of etodolac was enhanced by lidocaine about five times while that of diclofenac was not enhanced by lidocaine.

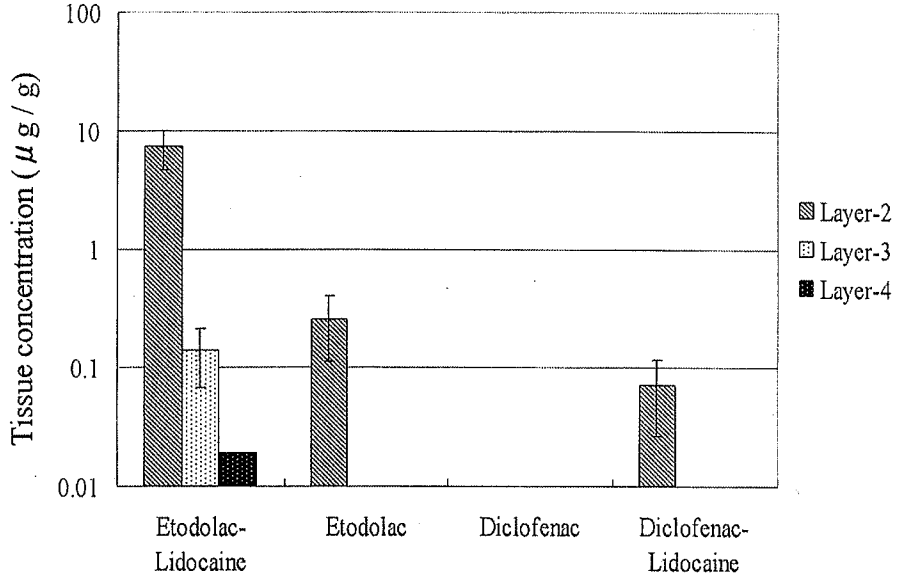
Comparison with Ketorolac



Transdermal absorption of ketorolac was not enhanced by lidocaine in the

similar manner to the case of diclofenac.

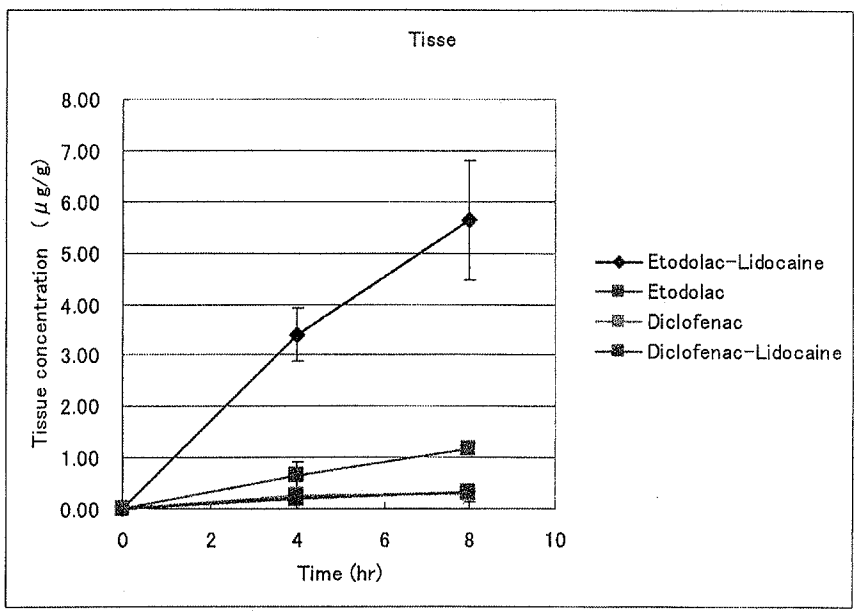
A-2) Penetratability and Diffusivity test in muscle tissue



As illustrated in the figure above, lidocaine enhanced penetratability and diffusivity of etodolac about 100 times compared with those of diclofenac in the second layer. In the third layer the penetration/diffusion of etodolac was observed in the present invention but the penetration/diffusion of diclofenac was not detected in the cited invention.

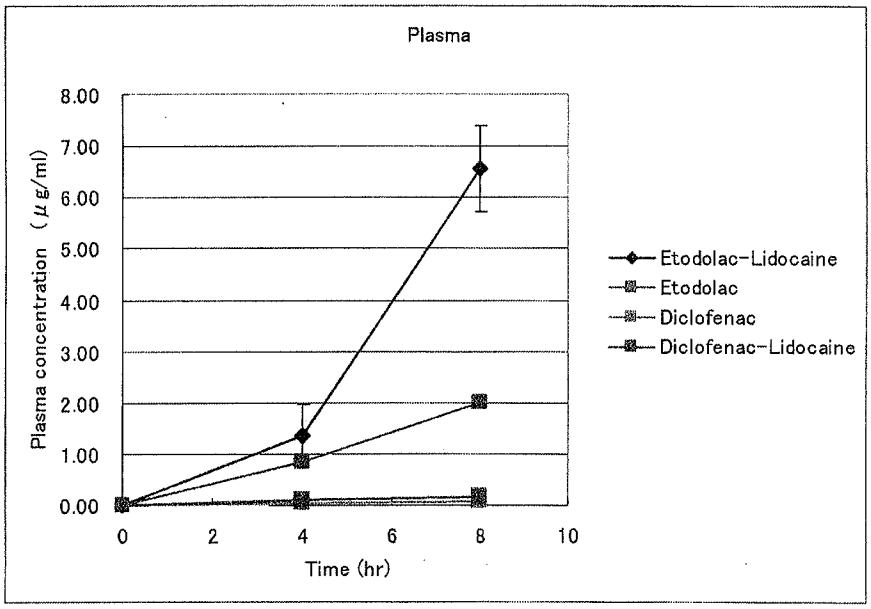
B. Evaluation *in vivo*

[Concentration of NSAID in muscle tissue]



In the present invention, Etodolac is penetrated and/or diffused about 17 times more efficiently than Diclofenac in the cited reference. Especially the penetratability and diffusivity of etodolac is about 5 times enhanced by lidocaine in the present invention while those of diclofenac in the cited reference are little enhanced by lidocaine.

[Concentration of NSAID in plasma]



Also in plasma concentration, a remarkable enhancing effect of lidocaine on transdermal absorption of etodolac compared with transdermal absorption of

diclofenac was confirmed.

4. Conclusion

Both of skin permeabiliy and penetratability/diffusivity in muscle tissue are totally reflected in concentration of NSAID in plasma. Compared to the formulation of diclofenac-lidocaine, about 41 times amount of NSAID (etodolac) was detected in plasma regarding the present invention (etodolac-lidocaine).

Lee et al. describes that a diclofenac salt of lidocaine is the preferred one in the various combination of NSAID and a local anesthetic(column 4, the 18th line); also diclofenac is replaceable with another NSAID and ketorolac is the preferred one among those NSAIDs (column 4, the 38th line). But, this experiment has shown that the enhancing effect of lidocaine on transdermal absorption of etodolac is remarkably more potent than the effect on diclofenac- or ketorolac-transdermal absorption.

Such an enhancing effect of lidocaine specific to etodolac is never expected from Lee et al. and I strongly believe the present invention is not obvious from Lee et al.

All statements made herein of my own knowledge are true and all statements made an information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

This 30th day of October, 2009

Hidetoshi Hamamoto

Hidetoshi HAMAMOTO